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Adulteration of herbal antidiabetic products with undeclared pharmaceuticals: a case series in Hong Kong

Chor Kwan Ching, Ying Hoo Lam, Albert Y. W. Chan & Tony W. L. Mak

Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Lai Chi Kok, Hong Kong, China

Correspondence
Dr Tony W. L. Mak MBChB, MBA, PgDip Medical Toxicology, FRCPA, FRCPath, Consultant Pathologist, Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Hong Kong, China.
Tel.: +852 2990 1987
Fax: +852 2990 1748
E-mail: makwl@ha.org.hk

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Proprietary Chinese medicines (pCMs), generally considered to be natural and harmless, are commonly used for many indications, including diabetes mellitus. Adulteration of pCMs with undeclared pharmaceuticals has been reported previously. However, a detailed study investigating the problem of adulterated herbal antidiabetic products and their associated toxicities is largely lacking.

WHAT THIS STUDY ADDS

- This study shows the severity of the under-recognized problem of adulteration of herbal antidiabetic products with undeclared pharmaceuticals, including both registered and banned drugs. Potentially fatal adverse effects could result from the use of these illicit products.

AIMS

The current study aims to examine the problem of adulteration of herbal antidiabetic products with undeclared pharmaceuticals, including both registered and banned drugs.

METHODS

All cases involving use of adulterated herbal antidiabetic products referred to a tertiary centre for clinical toxicology analysis from 2005 to 2010 inclusive were retrospectively reviewed. The patients' demographic characteristics, clinical presentations, medical history, drug history and the analytical findings of the herbal antidiabetic products were studied.

RESULTS

A total of 27 cases involving use of 29 adulterated herbal antidiabetic products were identified. Seventeen of the patients (63%) had clinical toxicities associated with the illicit products. Hypoglycaemia was the most common adverse effect, followed by lactic acidosis. Analysis of the 29 illicit herbal antidiabetic products revealed eight undeclared registered or banned oral antidiabetic agents, namely glibenclamide ($n = 22$), phenformin ($n = 18$), metformin ($n = 6$), rosiglitazone ($n = 6$), gliclazide ($n = 2$), glimepiride ($n = 2$), nateglinide ($n = 1$) and repaglinide ($n = 1$). Non-antidiabetic drugs were also detected in some products. Up to four adulterants were detected within the same product.

CONCLUSIONS

Adulteration of herbal antidiabetic products with undeclared pharmaceuticals is a significant yet under-recognized problem. Patients taking these illicit products could be at risk of potentially fatal adverse effects. It is important to educate the public to avoid taking pCMs of dubious source. Effective regulatory measures should be put in place to address the problem.

Introduction

Antidiabetic agents such as sulphonylureas, metformin, insulin, thiazolidinediones, and other new classes of medications constitute the cornerstone of medical management of type 2 diabetes mellitus [1]. However, many patients, particularly Chinese patients, also take Chinese medicine as an alternative or supplementary therapy. A variety of proprietary Chinese medicines (pCMs) marketed for the treatment of diabetes mellitus are particularly popular because of their convenience, perceived harmlessness and ready accessibility. Despite the claim of being purely herbal and safe, adulteration of these herbal antidiabetic products with different illicit agents, including undeclared prescription drugs and banned drugs, have been reported [2, 3]. Intake of these illicit products could result in significant morbidity and even mortality. Nevertheless, a detailed study investigating this problem is largely lacking. To examine this problem, the authors retrospectively reviewed cases involving use of herbal antidiabetic products adulterated with undeclared pharmaceuticals, referred to the centre from 2005 to 2010 inclusive.

Methods

From 2005 to 2010 inclusive, all cases involving use of adulterated, herbal antidiabetic products referred to the authors' centre, the only tertiary referral centre for clinical toxicology analysis in Hong Kong, were retrospectively reviewed. The patients were referred because of suspected poisoning or clinical suspicion of adulteration of pCMs with undeclared pharmaceuticals. Clinical data were obtained by reviewing the laboratory database and the patients' medical records. Demographic characteristics, clinical presentation, medical history, drug history and analytical findings of the herbal antidiabetic products were reviewed. The causal relationship between the patients' clinical features, if any, and the illicit agents detected in the products were evaluated according to the known adverse effects of the agents, the temporal sequence and the presence of other underlying diseases. The severity of any ascertained poisoning was graded by a previously published poisoning severity score [4].

The herbal antidiabetic products were analyzed qualitatively using high performance liquid chromatography with a diode array detector for general toxicology screen. Confirmatory tests using gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry were performed as required.

This study was approved by the Hong Kong Hospital Authority Kowloon West Cluster Research Ethics Committee (approval number KW/EX/11–066 (39–08)). The Committee exempted the study group from obtaining patient consent because the presented data are anonymous and the risk of identification is low.

Results

From 2005 to 2010 inclusive, a total of 27 cases involving use of adulterated herbal antidiabetic products were identified in the authors' centre. The cases were referred from 12 different local hospitals. The distribution of the cases over the years was as follow: three in 2005, two in 2006, four in 2007, four in 2008, five in 2009 and nine in 2010. Data from five of the cases have been previously published [3, 5]. Fourteen of the patients (52%) were males. Their age ranged from 31 to 90 years, with a median of 63 years. The reported duration of intake of the pCMs varied from 2 days to 2 years. Among the 25 patients who had diabetes mellitus, 14 patients had been prescribed with antidiabetic medications by doctors. However, four patients took the prescribed medications alongside the pCMs and the other 10 patients took only the pCMs. At the time of first prescription, the doctors did not know that their patients were also taking pCMs, or the patients did not take pCMs initially. The pCM drug history was obtained during subsequent medical follow-up or upon further questioning when the patients developed adverse effects. Of the remaining two patients, who did not have diabetes mellitus, one erroneously took the herbal antidiabetic products belonging to a relative and the other patient took the medication for general health promotion.

Twenty-nine illicit herbal antidiabetic products were received from the 27 patients. Eight different, undeclared oral antidiabetic agents of various classes were detected. Glibenclamide, found in 22 out of the 29 products (76%), was the most frequent adulterated drug, followed by phenformin in 18 (62%), metformin and rosiglitazone in six products each (21%), gliclazide and glimepiride in two each (7%) and nateglinide and repaglinide in one each (3%). Adulteration with non-antidiabetic drugs was also observed in five of the products. These drugs included hydrochlorothiazide, aminophenazone, cimetidine, diclofenac, domperidone, piroxicam, prednisolone acetate and tadalafil. Two of the illicit herbal antidiabetic products were adulterated with only non-antidiabetic drugs. The presence of more than one adulterant within the same product was frequently observed, with two products (7%) containing four adulterants, eight products (28%) containing three and 15 products (52%) containing two. Various markers of herbal ingredients were detected in 18 of the 29 products. The reported sources of the illicit herbal antidiabetic products, where available, included over the counter pharmacies, herbalists, relatives and friends, either locally or in mainland China. The combinations of adulterants in the 29 herbal antidiabetic products are listed in Table 1.

Table 1
Combinations of adulterants in the 29 illicit herbal antidiabetic products

Adulterant	Frequency of detection in pCMs	Combination of adulterants in pCMs
Glibenclamide	22 (76%)	Glibenclamide + phenformin (*n* = 10) Glibenclamide + phenformin + metformin (*n* = 4) Glibenclamide (*n* = 3) Glibenclamide + phenformin + metformin + aminophenazone (1) Glibenclamide + phenformin + rosiglitazone (*n* = 1) Glibenclamide + phenformin + gliclazide + domperidone (*n* = 1) Glibenclamide + rosiglitazone (*n* = 1) Glibenclamide + rosiglitazone + hydrochlorothiazide (*n* = 1)
Phenformin	18 (62%)	Glibenclamide + phenformin (*n* = 10) Glibenclamide + phenformin + metformin (*n* = 4) Glibenclamide + phenformin + metformin + aminophenazone (1) Glibenclamide + phenformin + rosiglitazone (*n* = 1) Glibenclamide + phenformin + gliclazide + domperidone (*n* = 1) Phenformin + rosiglitazone (*n* = 1)
Metformin	6 (21%)	Glibenclamide + phenformin + metformin (*n* = 4) Glibenclamide + phenformin + metformin + aminophenazone (1) Metformin + gliclazide (*n* = 1)
Rosiglitazone	6 (21%)	Glibenclamide + phenformin + rosiglitazone (*n* = 1) Glibenclamide + rosiglitazone (*n* = 1) Glibenclamide + rosiglitazone + hydrochlorothiazide (*n* = 1) Phenformin + rosiglitazone (*n* = 1) Rosiglitazone + glimepiride (*n* = 1) Rosiglitazone + glimepiride + nateglinide (*n* = 1)
Gliclazide	2 (7%)	Glibenclamide + phenformin + gliclazide + domperidone (*n* = 1) Metformin + gliclazide (*n* = 1)
Glimepiride	2 (7%)	Rosiglitazone + glimepiride (*n* = 1) Rosiglitazone + glimepiride + nateglinide (*n* = 1)
Nateglinide	1 (3%)	Rosiglitazone + glimepiride + nateglinide (*n* = 1)
Repaglinide	1 (3%)	Repaglinide (*n* = 1)*
Prednisolone acetate	1 (3%)	Prednisolone acetate + tadalafil (*n* = 1)
Tadalafil	1 (3%)	Prednisolone acetate + tadalafil (*n* = 1)
Diclofenac	1 (3%)	Diclofenac + piroxicam + cimetidine (*n* = 1)
Piroxicam	1 (3%)	Diclofenac + piroxicam + cimetidine (*n* = 1)
Cimetidine	1 (3%)	Diclofenac + piroxicam + cimetidine (*n* = 1)

*The antidiabetic product also contained glibenclamide, which was listed in the label, in addition to undeclared repaglinide.

Adverse effects related to the illicit agents detected in the herbal antidiabetic products were identified in 17 of the 27 patients (63%). Hypoglycaemia was the most common clinical presentation (*n* = 13) and lactic acidosis the second (*n* = 3). The severity of the 17 ascertained poisoning cases, as graded by the poisoning severity score, is shown as follows: severe (*n* = 2), moderate (*n* = 14) and minor (*n* = 1). Details of the clinical features, drug history and toxicological findings of the 17 poisoning cases are shown in Table 2.

Discussion

The present study, to the authors' knowledge, is the largest case series regarding adulteration of herbal antidiabetic products with undeclared pharmaceuticals. Previous reports showed that 23.7% of 2609 pCMs samples in Taiwan, where use of Chinese medicine is a common practice as in Hong Kong, and 7% of 260 pCMs samples collected from Californian outlets were adulterated with undeclared pharmaceuticals. However, oral antidiabetic agents were not common adulterants in these studies and glibenclamide was detected in only one out of the 2609 samples in Taiwan [6, 7]. A systemic review of world literature about adulteration of Chinese herbal medicines with synthetic drugs up till 2001 identified oral antidiabetic agents as adulterants in one case report and one analytical investigation report only [2], although the United States' Food and Drug Administration and Health Canada have also issued alerts on a few pCMs containing undeclared glibenclamide and phenformin in recent years [8, 9]. Compared with these previous reports, the authors' findings suggest that the problem of adulteration of herbal antidiabetic products may be more common than is generally acknowledged, particularly in the authors' locality.

Chinese medicine is generally believed by the lay public to be natural and harmless, particularly when compared with Western medications. However, this belief may not always hold true. In addition to the toxicity of some

Table 2

Summary of the 17 patients with adverse effects associated with intake of the adulterated herbal antidiabetic products

Gender/Age (years)	Name of pCM	Source of pCM	Duration of pCM use	Adulterated antidiabetic agents	Other adulterants	Associated adverse effects (severity)	Use of prescribed antidiabetic medication
F/73	Ku Le Kang	Unknown	2 months	Rosiglitazone, phenformin	Nil	Heart failure (moderate)	Not prescribed
M/56	Yi Su Kang Jiao Nang	OTC, mainland China	10 months	Glibenclamide, phenformin	Nil	Lactic acidosis (severe)	Prescribed but not taken
F/48	Jiang Tang Ning Jiao Nang	Unknown	3 months	Glimepiride, rosiglitazone, nateglinide	Nil	Hypoglycaemia (moderate)	Prescribed but not taken
F/79	Xiao Ke Shu Ping – Jiang Tang Ning Jiao Nang	Unknown	Unknown	Glibenclamide, phenformin, rosiglitazone	Nil	Hypoglycaemia (moderate)	Not prescribed
F/82	Unknown	OTC, Hong Kong	Unknown	Glibenclamide, phenformin	Nil	Hypoglycaemia (moderate)	Gliclazide
M/78	Unknown	Herbalist	>2 years	Glibenclamide, phenformin	Nil	Lactic acidosis (moderate)	Prescribed but not taken
M/58	Unknown	Friend	2 years	Glibenclamide, phenformin	Nil	Hypoglycaemia (moderate)	Prescribed but not taken
M/63	Tian Sheng Yi Bao	Mainland China	A few days	Glibenclamide, phenformin	Nil	Hypoglycaemia (moderate)	Not prescribed
M/71	Tang Le Shi Shen Jiao Nang	Mainland China	6 months	Glibenclamide, rosiglitazone	Nil	Hypoglycaemia (moderate)	Not prescribed
F/44	Yi Zhi Ren Jiao Nang	Relative	Unknown	Glibenclamide	Nil	Hypoglycaemia (moderate)	Not prescribed
M/64	Shen Ji Xi Jiao Wan	Unknown	Unknown	Glibenclamide, phenformin, metformin	Nil	Lactic acidosis, hypoglycaemia (severe)	Not prescribed
M/84	Ba Bao Xiao Ke Wan	Unknown	Unknown	Glibenclamide	Nil	Hypoglycaemia (moderate)	Gliclazide
F/66	Yi Huo Xiao Tang Ning Jiao Nang	Unknown	A few months	Glibenclamide, phenformin, metformin	Amino-phenazone	Hypoglycaemia (minor)	Prescribed but not taken
F/31	Unknown	Relative	Unknown	Gliclazide, metformin	Nil	Hypoglycaemia (moderate)	Not prescribed
M/59	Shen Shi Yi Huo Jiang Tang Ning Jiao Nang	OTC	A few years	Glibenclamide, phenformin	Nil	Hypoglycaemia (moderate)	Not prescribed
M/90	Yi Dao Pai Du Jiao Nang Jing Xue Wen Tang Jiao Nang	Mainland China Mainland China	2 days 2 days	Glibenclamide, phenformin Nil	Nil Prednisolone acetate, tadalafil	Hypoglycaemia (moderate)	Not prescribed
M/58	Tang Ke Wan	Unknown	1 month	Nil	Diclofenac, piroxicam, cimetidine	Renal impairment (moderate)	Prescribed but not taken

well reported poisonous Chinese medicines, such as aristolochic acid containing herbs and aconite herbs [10, 11], adulteration of pCMs with undeclared pharmaceuticals is another safety issue requiring attention. The occurrence of pronounced poisoning symptoms in a large proportion of the cases illustrated the danger of taking such adulterated herbal antidiabetic products. Hypoglycaemia was the most commonly encountered adverse effect. Eleven of the 13 patients who developed hypoglycaemia took only pCMs but not the other prescribed medications for diabetes mellitus, suggesting that the adulterated pCMs were likely the sole cause. Sulphonylureas, with the highest risk of hypoglycaemia among various oral antidiabetic agents, were detected in all herbal antidiabetic products implicated in these hypoglycaemia cases. Other co-adulterants, including phenformin, metformin, rosiglitazone and nateglinide, were also detected in 11 of these 13 products.

The reported mortality rate of biguanide-induced lactic acidosis is as high as 50.3% [12]. Although all biguanides can cause lactic acidosis, phenformin is associated with the highest risk, leading to its withdrawal from the market in many countries. The reported incidence of phenformin-induced lactic acidosis was 0.64 cases/1000 patient-years, an order of magnitude higher than that of metformin [13]. Despite the widespread ban of phenformin, the drug is still available from different sources, including adulterated pCMs. Phenformin was the second most common adulterant in the present study; three of the 18 patients who had taken pCMs adulterated with phenformin developed potentially fatal lactic acidosis. Metformin, in addition to phenformin, was also detected in one of the products implicated in biguanide-induced lactic acidosis. Heart failure related to undeclared rosiglitazone, which developed in one patient, was yet another example of a banned or restricted drug escaping control and continuing to pose a risk to the consumer [14, 15].

Unexpectedly, non-antidiabetic agents were detected in five herbal antidiabetic products and they were the only adulterants in two products. The labels of these two pCMs clearly indicated that the products had an effect on diabetes mellitus. These other adulterants, such as prednisolone acetate and non-steroidal anti-inflammatory drugs (NSAIDs), could also cause significant toxicities. The reason for adding non-antidiabetic drugs to the herbal antidiabetic products remains obscure. The authors postulate that poor quality control systems during production and error in the manufacturing process are possible causes. It is likely that multiple types of pCMs adulterated with different pharmaceuticals for various disease indications are synthesized together in each illicit pCM manufacturing plant with questionable quality systems, and hence there is the chance for error or contamination during production. Indeed, there was an outbreak of hypoglycaemia in 2009 caused by adulteration of sexual enhancement products with sildenafil and also, in this case sildenafil, with glibenclamide, and the latter is not known to have any sexual enhancement effect [16].

Detection of multiple adulterants in a single product is a common finding. In addition, as Chinese medicine is generally considered to be good for health, the patients may take more than one illicit pCM, which could again contain multiple adulterants. They may also take prescribed antidiabetic drugs together with the illicit pCM. All these factors may lead to significant overdose and possible drug–drug or drug–herb interactions, exponentially compounding the danger of taking such adulterated pCMs.

Patients taking adulterated herbal antidiabetic products may also have poor diabetic control. Such adulterated pCMs may give a false impression that these preparations are effective, and hence the patients may stop taking the prescribed antidiabetic medications or even default medical follow-up, as observed in 10 out of the 14 patients who had been previously prescribed various antidiabetic agents.

All cases in this study were referred to the authors' centre because of poisoning features or suspected pCM adulteration. As a result, the data cannot reflect the exact prevalence of such illicit pCMs in the market, but they point to a serious problem. Besides, the rising trend, with one-third of the cases being identified in the past year, may indicate an escalating severity of the problem or increasing awareness of healthcare professionals. Not only are pCMs widely used in Chinese communities around the world, but they are also gaining popularity in Western countries [17]. Moreover, pCMs are readily accessible over the counter and also worldwide through the Internet. It is expected that use of these illicit pCMs for diabetes mellitus and the associated potentially life-threatening toxicities will increasingly occur in many other countries. Regulatory bodies should be aware of this phenomenon and take effective measures to combat this illegal practice. The public should be educated about the risk of pCM adulteration. A detailed drug history, including Chinese medicine, and comprehensive laboratory analysis of relevant specimens can help to confirm the diagnosis in poisoning cases.

In conclusion, we have reported a case series involving the use of 29 herbal antidiabetic products adulterated with various registered or banned pharmaceuticals, with significant toxicities occurring in a large proportion of the patients. These illicit pCMs, disguised as natural and harmless products, pose severe health hazards to the public. It is important to educate the public to avoid taking pCMs from dubious sources. Effective regulatory measures should be implemented to address this significant, yet under-recognized problem.

Competing Interests

There are no competing interests to declare.

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